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METHOD AND APPARATUS FOR ARCHIVING BIOLOGICAL SAMPLES IN A SOLID STATE MANNER

BACKGROUND OF THE INVENTION

The related fields of pharmacogenomics and genetic epidemiology have matured rapidly as a spin-off from the human genome project. Single nucleotide polymorphism (SNP) data are accumulating at a rapid pace, due to re-sequencing of the human genome. Large-scale SNP discovery initiatives in the U.S. and particularly in Japan are defining high variability in the genetic make-up of the human population, at the nucleotide level.

These SNP studies are confirming what had been hypothesized earlier from genetic epidemiology: namely that the human population possesses high functionally and significant variability in the genes that may be responsible for the response to medication (pharmacogenomics) and absolute disease risk (genetic epidemiology). The scientific challenge will be to discover the exact relationship between genetic variability and risk, or the response to medication, from the gene panels that define the responsible biochemical pathways.

Of necessity, the process that can lead to the desired pharmacogenomic or epidemiological correlations requires the study of gene polymorphism in very large human sample sets, possibility as large as 100,000 to 500,000, in a fashion which allows rapid, random access to DNA from such samples at rates that may approach 10,000 samples per day. Technology has been developed, based upon DNA microarrays and other methods such as high throughput mass spectrometry, which would allow such a large number of genotype (SNP) tests to be performed per day. All such technologies require processing of samples from their crude state (whole blood for instance) to produce purified DNA that can be used for the desired PCR or equivalent gene amplification reaction.

As a result of the above scientific and biotechnical advances, a bottleneck has developed, relative to the storage and rapid, random-access retrieval of DNA from the required large sample libraries. No current technology can serve that purpose.

The ideal technology would be one in which samples of interest could be transferred easily and cheaply (in the field or in the clinic) to a highly standardized sample storage format, stored inexpensively, permanently, and then retrieved easily in a PCR-ready state, at a rate of up to 10,000 samples per day per storage facility. Optionally, bar coding of the samples may be employed.

Recently, several groups have described the development of two-dimensional paper substrates, which are suited for large scale sample archiving. Unprocessed sample material can be placed on the paper, cells will lyse, and DNA will "stick" to the paper firmly enough that contaminants can be removed from the paper with hot water or detergent washing. Examples of sample material include whole blood, blood serum, blood plasma, blood lymphocytes, fixed or unfixed tissue extracts, buccal scrapes, DNA, RNA or protein. Examples of paper useful for the invention are manufactured by Whatman (FTA), S&S and other suppliers. The paper can be imbedded with agents to prohibit the growth of mold or bacteria during long periods of storage at room temperature and humidity.

The key technology component lacking in those paper storage technologies is the ability to automate sample storage and the automation of the sample retrieval process. This lack of automation has not been a limitation thus far, since the primary application of such paper has been in forensics, which does not generally require repeated access to the samples. Ideally, the largest archives using the paper to date (the FBI and Armed Forces) would seldom, if ever, retrieve the stored samples. For that reason, automation that would allow for rapid, random-access and processing of such samples is not known to be practiced.

In contrast, the requirements of pharmacogenomics and genetic epidemiology are much more rigorous with respect to rapid storage and retrieval ("I/O") of such biological samples. Thus, in order to enable the large scale archiving and analysis of human samples, it has been necessary to develop integrated engineering solutions, that allow this kind of paper storage format to be accessed quickly, accurately and repeatedly over time.

DETAILED DESCRIPTION OF THE INVENTION

The preferred solution to the sample storage problem is the constraint of the binding medium (FTA being an example) inside a rigid or semi rigid frame, much like photographic sides are constrained within a rectangular frame in order to be processed by a 35mm slide projector.

For a specific DNA genotyping embodiment, each "35mm" DNA paper slide would accommodate an amount of blood or another biological sample of sufficient size to support numerous individual PCR gene amplification reactions. Here the DNA slides would be automatically punched by a robot to yield numerous "pellets", each about 1mm in diameter. The biological storage medium, or paper, would be held firm by a "slide carrier" analogous to the slide carriers used for optical projection, and hence have the capacity to organize the biological slides in a way that can be stored compactly and retrieved as needed from a library. (Figure 1)

The invention would facilitate automation to allow random access of individual slides within a carrier and remove each slide for presentation. No automation of such kind has yet been described in the area of sample handling and retrieval. Further modifications may include particular size and shape or material of construction of the slide "mount" or the size or shape of the "carrier" for such slides. In addition, the general technique for random access of slides within a holder is also envisioned.